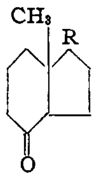
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of *cis* and *trans* 1-Methyl-cyclopentane-1,2-dicarboxylic Acids and Related Compounds

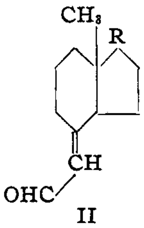
BY W. E. BACHMANN AND W. S. STRUVE[1]

Hexahydroindanone derivatives of the type I have been obtained as products of the oxidation of the antirachitic vitamins D_2 and D_3. Thus, by oxidation of vitamin D_2 in acidic solution Windaus and Grundmann[2] obtained a ketone of this structure in which R = $CH(CH_3)CH{=}CHCH(CH_3)CH(CH_3)_2$, the C_{17} side chain of ergosterol, and from vitamin D_3 Windaus, Deppe, and Wunderlich[3] obtained a similar ketone in which R = $CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$, the C_{17} side chain of cholesterol. From the chromic acid oxidation products of vitamin D_2 Heilbron and co-workers[4] were able to isolate the α,β-unsaturated aldehyde II [R = $CH(CH_3)CH{=}CHCH(CH_3)CH(CH_3)_2$]. These compounds proved useful in confirming the structure of the vitamins.

We have undertaken the synthesis of compounds of this type for it appeared that they would prove useful intermediates in the synthesis of the vitamins. Attention has been directed to the preparation of the ketones (I) for it should be possible to prepare the unsaturated aldehydes from them. In order to explore the possibilities of this method for synthesizing the antirachitic vitamins, we set out to prepare 4-keto-7a-methylhexahydroindane (I, R = H), an analog possessing the characteristic angular methyl group but lacking the side chain present in the vitamins. Although our goal has not yet been reached, we are reporting the progress that has been made up to the present time.



I



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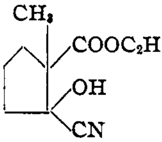
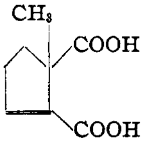
The method designed to yield a ketone of the desired structure consisted in the preparation of 1-methylcyclopentane-1,2-dicarboxylic acid (V) followed by the construction of the cyclohexanone ring. The intermediate dicarboxylic acid (IV) was prepared by the method employed by Linstead and Millidge[5] to obtain the corresponding cyclohexene derivative. In this synthesis, 2-methyl-2-carboethoxycyclopentanone was converted to the cyanohydrin (III) by means of liquid hydrogen cyanide. The cyanohydrin was dehydrated by means of thionyl chloride and pyridine and the unsaturated nitrile was hydrolyzed to the unsaturated dicarboxylic acid (IV). The over-all yield for the three steps was 79%.

The unsaturated acid was hydrogenated rapidly in the presence of Adams catalyst to give a mixture of *cis* and *trans* 1-methylcyclopentane-1,2-dicarboxylic acid (V). Although part of the mixture solidified, it was not possible to effect a separation of the two acids by recrystallization. When the mixture of acids was refluxed with an excess of acetic anhydride, the anhydride of what is probably the *cis* acid was formed, from which the *cis* acid was prepared by hydrolysis. The *trans* acid was prepared by esterifying the mixture of acids and heating the esters with an alcoholic solution of sodium ethoxide, a procedure used by Hückel and Goth[6] to obtain the *trans* form of cyclohexane-1,2-dicarboxylic acid from the *cis* isomer. By this procedure it was possible to



III



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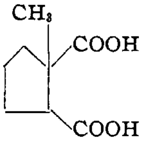
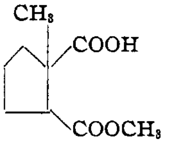
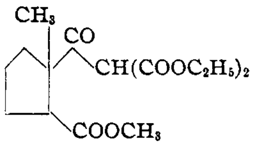


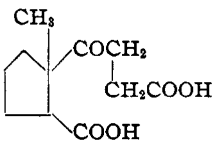
V



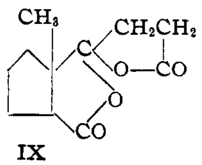
VI



VII



VIII



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[1] Du Pont Post-Doctoral Fellow.

[2] Windaus and Grundmann, *Ann.*, **521**, 160 (1935).

[3] Windaus, Deppe, and Wunderlich, *ibid.*, **533**, 118 (1937).

[4] Heilbron, Jones, Samant and Spring, *J. Chem. Soc.*, 905 (1936).

[5] Linstead and Millidge, *ibid.*, 478 (1936).

[6] Hückel and Goth, *Ber.*, **58**, 447 (1925).

transform our pure *cis* acid to the *trans* acid, and by means of acetic anhydride the pure *trans* form was converted to the anhydride of the *cis* acid.

After our investigations had been completed, we read that Dutta[7] had prepared the *cis* and *trans* forms of V. Dutta reported that he had obtained the *trans* acid by reducing the unsaturated acid (IV) by sodium amalgam and water. Apparently he was unable to effect the conversion of the *trans* acid to its diastereoisomer for he prepared the *cis* acid by an entirely different synthesis. The properties of his compounds agreed with those of ours in all respects.

By reaction of the *cis* anhydride with methanol an acid ester was formed which by analogy with similar compounds[8] must be *cis*-1-methyl-1-carboxy-2-carbomethoxycyclopentane (VI) in which the tertiary carboxyl group is left unesterified. The acid chloride was condensed with magnesio malonic ester to give the substituted malonic ester VII. By reaction of the sodio derivative of this compound with methyl bromoacetate an acetic acid residue was introduced. Hydrolysis of the resulting product with a mixture of hydrochloric and acetic acid did not give the acid VIII but a compound which contained a molecule of water less than the acid. The compound is most likely a dilactone[9] possessing the structure IX. The formation of an acid anhydride under the conditions employed seems to us less likely. The compound does not dissolve in sodium carbonate solution but does dissolve in hot aqueous sodium hydroxide. The acid can be obtained—accompanied by some of the dilactone—by acidifying the cold solution of the sodium salt. When a hot solution of the salt is acidified, the dilactone is the sole product. By treatment with methanolic hydrochloric acid, the dilactone is converted to the dimethyl ester of VIII. It is planned to reduce the keto group of the acid or its ester and cyclize the resulting dicarboxylic acid to yield I (R = H). The keto group, however, has proved to be very resistant to reduction. Of the various methods that have been tried, catalytic reduction of the ester appears to be the most promising. This is now being investigated.

Experimental

1 - Methyl - 1 - carboethoxy - 2 - hydroxy - 2 - cyanocyclopentane (III).—Following the procedure employed by Linstead and Millidge[5] on the corresponding cyclohexane analog, 250 g. of 2-methyl-2-carboethoxycyclopentanone was added drop by drop to a mixture of 160 cc. of hydrogen cyanide and 2 cc. of 45% aqueous potassium hydroxide cooled in an ice-salt mixture. After standing in a refrigerator overnight, the mixture was acidified with concentrated sulfuric acid, the excess of hydrogen cyanide was removed under reduced pressure and the residue was distilled; b. p. 115–116° at 2 mm. (reported,[7] 122° at 4 mm.); yield, 266 g. (92%) of colorless liquid.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.9; H, 7.6. Found: C, 60.9; H, 7.7.

1 - Methyl - 1 - carboethoxy - 2 - cyanocyclopentene-2.—To a mixture of 266 g. of the above cyanohydrin and 216 cc. of pyridine cooled in a freezing mixture was added drop by drop 195 cc. of thionyl chloride. The mixture was then warmed on a steam-bath for one hour, ice and hydrochloric acid were then added, and the aqueous layer was extracted with ether. The ether extracts were washed with 10% sodium hydroxide solution and dried with anhydrous sodium sulfate. The residue obtained by removal of the ether was distilled under reduced pressure; b. p. 101–104° at 2 mm. (reported,[7] 100–102° at 4 mm.); yield, 224 g. (92%) of a yellow liquid. The yellow color is due to the presence of sulfur which could not be removed completely from the cyanide. As a result the product was not analytically pure.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3. Found: C, 65.8; H, 7.2.

1-Methyl-2-cyclopentene-1,2-dicarboxylic Acid (IV).—A mixture of 224 g. of the above cyanide and 800 cc. of concentrated hydrochloric acid was refluxed for twenty-four hours. After the mixture had been cooled, the colorless acid was filtered. A further quantity of less pure acid was obtained by evaporation of the mother liquor; total yields, 197 g. (93%); m. p. 201–204°. After several recrystallizations from acetic acid the melting point was 203–204° (reported,[7] 203–204°).

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.5; H, 5.9. Found: C, 56.8; H, 6.0.

A mixture of 3 g. of the above unsaturated acid and 15 cc. of acetic anhydride was refluxed for two hours. The acetic anhydride was removed under reduced pressure and the residue was distilled; b. p. 113–115° at 0.6 mm.; yield, 1.79 g. (67%). The resulting **1-methyl-2-cyclopentene-1,2-dicarboxylic acid anhydride** was obtained as a colorless liquid which solidified on cooling to a colorless solid; m. p. 30–32.5°.

Anal. Calcd. for $C_8H_8O_3$: C, 63.1; H, 5.3. Found: C, 62.8; H, 5.3.

A mixture of 1.79 g. of the above anhydride and 15 cc. of absolute methanol was refluxed for two hours. The methanol was removed under reduced pressure and the residue

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[7] Dutta, *Science and Culture*, **6**, 570 (1940); *C. A.*, **34**, 6933 (1940).

[8] Compare the reaction of camphoric acid anhydride [Bruhl and Braunschweig, *Ber.*, **26**, 285 (1895)] and 2,2-dimethylsuccinic anhydride [Bone, Sudborough and Sprankling, *J. Chem. Soc.*, **85**, 547 (1904)] with methanol; in these reactions the tertiary carboxyl group is not esterified.

[9] Examples of similar lactones are the dilactone of 2,2′-benzophenone-dicarboxylic acid and its derivatives [Graebe and Juillard, *Ann.*, **242**, 244 (1887)], hydrocheldonic anhydride [Michael, *J. prakt. Chem.*, [2] **44**, 118 (1891)] and the dilactone of α,ϵ-dimethyl-γ-ketosuberic acid [Sutter and Wijkman, *Ann.*, **519**, 97 (1935)].

was crystallized from acetone–petroleum ether; m. p. 113–115°; yield, 1.15 g. (53%). After several recrystallizations from acetone–petroleum ether the **1-methyl-1-carboxy-2-carbomethoxycyclopentene** was obtained as colorless irregularly hexagonal prisms; m. p. 115–116°.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.7; H, 6.5. Found: C, 58.5; H, 6.6.

Mixture of *cis* and *trans*-1-Methylcyclopentane-1,2-dicarboxylic Acid.—A mixture of 20 g. of 1-methyl-2-cyclopentene-1,2-dicarboxylic acid, 0.1 g. of Adams platinum catalyst and 100 cc. of absolute alcohol was shaken under a slight hydrogen pressure until the theoretical amount of hydrogen had been absorbed, which generally required about two hours. Trituration of the oily residue obtained by evaporation of the filtered alcohol solution with acetone and petroleum ether gave 14 g. of crystalline product; m. p. 108–113°. This melting point varied over three or four degrees with different runs. Crystallization from benzene–petroleum ether, chloroform–petroleum ether, or acetone–petroleum ether did not appreciably change the melting point. The acid is readily soluble in alcohol, ether and water.

***cis*-1-Methylcyclopentane-1,2-dicarboxylic Acid** (V).—A mixture of 102 g. of the oily mixture of *cis* and *trans* acids obtained in the hydrogenation and 500 cc. of acetic anhydride was refluxed for three hours. The acetic anhydride was removed under reduced pressure and the residue was distilled; b. p. 105–108° at 6 mm. (reported,[7] 101° at 4 mm.); yield, 68 g. (75%). The ***cis*-1-methylcyclopentane-1,2-dicarboxylic acid anhydride** was a semisolid which looked like freshly precipitated silica gel.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.3; H, 6.5. Found: C, 62.1; H, 6.6.

A mixture of 5 g. of *cis* anhydride, 6 cc. of 45% potassium hydroxide solution and 6 cc. of water was heated on a steam-bath until the anhydride had dissolved. The solution was acidified and evaporated to dryness. The residue was extracted with benzene and acetone, the solvents were evaporated and the *cis* acid was crystallized from benzene–petroleum ether; m. p. 117–122°; yield, 3.44 g. (62%). After several recrystallizations from benzene–petroleum ether colorless rectangular prisms of the *cis* acid were obtained; m. p. 128–129° (reported,[7] 123–125°) when put into a bath at 110°. When heated slowly, the *cis* acid melted at 117–119°.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.8; H, 7.0. Found: C, 56.0; H, 7.0.

Conversion of *cis*-1-Methylcyclopentane-1,2-dicarboxylic Acid to the *trans* Acid.—The dimethyl ester prepared from 1 g. of the *cis* acid by means of diazomethane was refluxed in a solution of sodium methoxide prepared from 3 g. of sodium and 75 cc. of methanol for twelve hours. Fifty cc. of water was then added and the whole was refluxed for four hours longer. As much alcohol as possible was removed by distillation, the aqueous residue was acidified with hydrochloric acid, the water was removed under reduced pressure, and the residue was extracted with acetone and ether. The residue obtained by evaporation of the organic extracts was crystallized from benzene–petroleum ether; m. p. 140–141°; yield, 0.54 g. (54%). After two recrystallizations from benzene–petroleum ether, clusters of small colorless needles of the *trans* acid were obtained; m. p. 142–143.5° alone and when mixed with authentic *trans* acid.

***trans*-1-Methylcyclopentane-1,2-dicarboxylic Acid** (V).—Two grams of the crystalline mixture of *cis* and *trans* acids was esterified with ethereal diazomethane. The ester was treated with sodium methoxide and worked up exactly as in the preceding preparation; m. p. 110–130°; yield, 1.35 g. (78%). After several recrystallizations from benzene–petroleum ether colorless needles were obtained; m. p. 142–143.5° (reported,[7] 142°).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.8; H, 7.0. Found: C, 55.7; H, 7.0.

A mixture of 0.5 g. of the crystalline mixture of *cis* and *trans* acids and 5 cc. of concentrated hydrochloric acid was heated in a sealed tube at 180° for ten hours. The resulting clear yellowish solution was evaporated to dryness. Trituration of the residue with petroleum ether gave 0.3 g. of product melting at 102–125°. After several crystallizations from benzene–petroleum ether the acid melted at 142–143° alone and when mixed with the *trans* acid obtained by the action of sodium methoxide on the mixture of *cis* and *trans* esters.

Several attempts were made to prepare the acid ester of the *trans* acid in which the tertiary carboxyl group was not esterified. By refluxing the *trans* acid with 2.5% methanolic hydrochloric acid, only the alkali-insoluble dimethyl ester could be isolated if the esterification was allowed to proceed longer than two hours. If the esterification was stopped at the end of a half hour, a mixture of diester and free acid was obtained but no half ester could be isolated. By refluxing equimolecular amounts of *trans* acid and methanol in ethereal hydrochloric acid mixtures of diester and free acid were obtained but no half ester could be found.

Conversion of *trans*-1-Methylcyclopentane-1,2-dicarboxylic Acid to the *cis* Acid.—A mixture of 2 g. of the *trans* acid and 8 cc. of acetic anhydride was refluxed for fifteen hours. The residue obtained by removal of the acetic anhydride under reduced pressure was distilled; b. p. 105–108° at 7 mm.; yield, 0.90 g. The *cis* anhydride (which did not set to a gelatinous mass) was warmed with 2 cc. of 45% potassium hydroxide solution and 5 cc. of water until the anhydride dissolved. The residue obtained by removal of the water from the acidified solution was extracted with acetone and ether, the solvents were evaporated and the product was crystallized from benzene–petroleum ether; m. p. 119–122°; yield, 0.72 g. After several recrystallizations from benzene–petroleum ether the *cis* acid melted at 123–124.5° alone and when mixed with authentic *cis* acid.

***cis*-1-Methyl-1-carboxy-2-carbomethoxycyclopentane** (VI).—A mixture of 25 g. of the above anhydride and 200 cc. of absolute methanol was refluxed for three hours. The methanol was removed under reduced pressure, the theoretical amount of acid ester remaining as a colorless liquid. Attempts to distill the compound under reduced pressure gave the anhydride and we were unable to purify the compound further.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.0; H, 7.5. Found: C, 57.8; H, 7.5.

Diethyl *cis*-1-Methyl-2-carbomethoxycyclopentanoylmalonate (VII).—To a solution of 15 g. of the above acid ester (VI) in 20 cc. of dry ether and 4 drops of pyridine was added 15 cc. of thionyl chloride. After standing at room temperature for one hour, the ether and excess thionyl chloride were removed under reduced pressure. The acid chloride was dissolved in 50 cc. of dry ether and added to a solution of magnesio malonic ester in 100 cc. of ether prepared from 30 cc. of malonic ester and 4.7 g. of magnesium.[10] After refluxing overnight, the mixture was treated with dilute hydrochloric acid, the ethereal layer was washed with dilute sodium carbonate solution, the ether was evaporated, and the residue was distilled under reduced pressure; b. p. 170–172° at 0.4 mm.; yield, 21.1 g. (80%). The substituted malonic ester was obtained as a colorless liquid which gave a reddish-brown color with alcoholic ferric chloride.

Anal. Calcd. for $C_{16}H_{24}O_7$: C, 58.5; H, 7.3. Found: C, 58.2; H, 7.0.

cis-γ-1-**Methyl-2-carboxycyclopentyl-γ-ketobutyric Dilactone (IX)**.—To a solution of sodium ethoxide prepared from 1.33 g. of sodium and 30 cc. of absolute alcohol was added 19 g. of the above malonic ester. After the mixture had stood at room temperature for ten minutes, 10 cc. of methyl bromoacetate was added. The mixture was allowed to stand at room temperature overnight and then was refluxed for one hour. Dilute hydrochloric acid was added to the cooled mixture and the precipitated oil was taken up in benzene. The benzene solution was washed with water and the benzene was evaporated. The residue was refluxed for forty-eight hours with a mixture of 50 cc. of acetic acid and 100 cc. of concentrated hydrochloric acid. The hydrochloric and acetic acids were removed under reduced pressure and the residue was taken up in benzene. The benzene was washed with 10% sodium carbonate solution and then with water. The residue obtained by evaporation of the benzene was crystallized from benzene–petroleum ether; m. p. 152–153.5°; yield, 5.5 g. (45%). After several recrystallizations from benzene–petroleum ether the dilactone was obtained as colorless needles; m. p. 155–156°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.7; H, 6.7. Found: C, 62.9; H, 6.9.

The *cis*-γ-**1-methyl-2-carboxycyclopentyl**-γ-**ketobutyric acid (VIII)** was obtained by heating 3 g. of the dilactone in 4 cc. of 45% potassium hydroxide solution and 10 cc. of water until a clear solution was obtained. The solution was cooled in ice water and was acidified with dilute hydrochloric acid. The acidified solution was extracted with ether. The residue obtained by evaporation of the ethereal extract was crystallized from benzene–petroleum ether; m. p. 113.5–114.5°; yield, 2.2 g. (73%). The oily residue from the mother liquor can be reworked in the same manner and a further quantity of the free acid can be obtained. After several recrystallizations from benzene–petroleum ether the acid was obtained as colorless prisms; m. p. 114.5–115°.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.9; H, 7.0. Found: C, 58.3; H, 7.2.

Methyl *cis*-γ-**1-Methyl-2-carbomethoxycyclopentyl**-γ-**ketobutyrate.**—A mixture of 2 g. of the dilactone and 40 cc. of 2.5% methanolic hydrochloric acid was refluxed for twenty-four hours. The methanol was removed under reduced pressure, benzene was added, and the benzene solution, after being washed with dilute sodium carbonate solution, was evaporated and the residue was distilled, giving the methyl ester as a colorless liquid; b. p. 172–174° at 0.6 mm.; yield, 2.13 g. (87%).

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.0; H, 7.8. Found: C, 60.6; H, 78.

Summary

Some intermediates in a proposed synthesis of 4-keto-7a-methylhexahydroindane are described.

ANN ARBOR, MICHIGAN RECEIVED JANUARY 7, 1941

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(10) Lund, *Ber.*, **67**, 935 (1934).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF WASHINGTON]

Raman Spectra of Aldehyde and Ketone Bisulfites

BY C. N. CAUGHLAN AND H. V. TARTAR

The structure of aldehyde and ketone bisulfites has, until recent years, been an open question. Since only one investigator has used a physical method for determining the constitution of these addition products,[1] it was deemed a worthy undertaking to determine, if possible, the type of valence bonds by means of the Raman effect.

The aldehyde and ketone bisulfites have been considered to be salts of either, (1) hydroxysulfonic acids, or (2) esters of sulfurous acid. The first structure was assigned in the beginning. Later this was abandoned because of Müller's[2] reported preparation of potassium hydroxymethanesulfonate by sulfonating methyl alcohol, which showed entirely different properties from the corresponding formaldehyde bisulfite.[3] Raschig and Prahl[4] found that the product obtained by Müller was actually dipotassium *sym*-acetonedisulfonate, formed from acetone as an impurity in the methyl alcohol used. In addition they showed that sulfonation of methyl alcohol produces methyl hydrogen sulfate, an isomer of hydroxy-

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(1) Stelling, *Cellulosechem.*, **9**, 100–102 (1928).

(2) Müller, *Ber.*, **6**, 1031 (1873).

(3) Reinking, Dehnel and Labhardt, *ibid.*, **38**, 1069 (1905).

(4) Raschig and Prahl, *ibid.*, **59**, 2025–2028 (1926).